

Glycol ethers P-series category

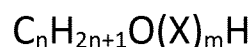
1. Category definition and its members

1.1 Category hypothesis

This category covers P-series glycol ethers that are produced by the reaction of propylene oxide (PO) with primary alcohols in the range C1-C4 (methanol, ethanol, n-propanol and n-butanol) in the presence of a base catalyst (as opposed to E-series glycol ethers that are produced with ethylene oxide). Chain prolongation occurs by further reaction of the glycol ether with excess propylene oxide during the production process. Therefore, a mixture of mono-, di-, tri- and higher propylene glycol ethers are formed, which are separated from each other by distillation.

Category members can have one or more PO 'monomer' units in them, although the maximum number for discrete molecules is four in commercial products. Molecules containing higher numbers of PO units do exist but these are only normally present as impurities or minor components of the higher molecular weight substance streams from production processes. The category is characterised by the presence of one or more ether groups and a single hydroxyl group.

The generic structure is therefore:



where n is 1 to 4 and m is typically 1 to 4

X = either (a): $\text{CH}_2\text{CH}(\text{CH}_3)\text{O}$ or (b): $\text{CH}(\text{CH}_3)\text{CH}_2\text{O}$

where (a) is the dominant form resulting in a secondary terminal hydroxyl group

The P-series glycol ethers in the category contain various distinct isomers. Propylene glycol mono-alkyl ethers contain 2 isomers. The reaction kinetics involved in the manufacturing of these glycol ethers favours the production of 1-alkoxy-2-propanol (α -isomer) over the corresponding 2-alkoxy-1-propanol (β -isomer) such that the level of β -isomer makes up less than 5% in the commercial product. By changing reactions conditions and by distillation the level of the β -isomer can be further reduced, e.g. in commercial propylene glycol mono-methyl ether the level of the β -isomer is <0.3%. The di-propylene and tri-propylene glycol alkyl ethers are mixtures of 4 and 8 isomers (RR and RS enantiomers), respectively.

Annex IX, paragraph 1.5 of the REACH legislation describes the criteria for grouping of substances and read-across: substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group or "category" of substances. For P-series glycol ethers, considered in this document, most end points are data rich and many contain multiple data points, and have common functional groups and common metabolic pathways. This enables the identification of trends in physicochemical and toxicological properties across the homologous series and thus justifies the category approach. A case-study with a number of P-series glycol ethers was recently conducted by Vink *et al* (2010) to assess the use of read-across and a tiered exposure

assessment in risk assessment under REACH. This study showed that a robust category with a sufficient set of data can adequately be used to accurately predict the toxicity for members of the category where data are not available. Specifically this work demonstrated that read across within the P-series category is robust and justified.

1.2 Applicability domain of the category

The category is limited to propylene oxide based glycol ethers. The scope is limited to those made using linear alcohols up to C4 as there is no data beyond this and no need to extend the category beyond this point. The category applies to glycol ethers containing up to four linked propylene oxide units. Three commercial important acetate esters of methanol- and ethanol based propylene glycol ethers have also been included in this paper. The acetates rapidly hydrolyse to the parent glycol ethers and therefore, their toxicological properties are comparable with those of the corresponding glycol ethers (for details, see below). The category does not cover glymes (molecules containing two alcohol units and characterised by no hydroxyl functionality).

1.3 Category members

The available data should be considered in the context of which of the P-series glycol ethers are commercially important. These are shown below. Blocked out cells in red are members of the category which are not in commerce. The blocked out cell in green is defined as a polymer and does not require registration under REACH according to the 2007 legislation. In addition, the table also shows the dates when REACH registration dossiers have been or will be submitted for each substance.

PROPERTY:	COMMERCIALY IMPORTANT MEMBERS OF THE CATEGORY			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	2010	2010	2010	2010
Mono-acetate	2010	2010		
Di	2010	2010	2013	2010
Di-acetate	2010			
Tri	2010			2010
Tetra*				2010

*Not in pure form but as a mixture of tri, tetra and heavier members of the series. The tetra-heavies for butyl have been submitted under REACH as a UVCB substance covering process streams that are primarily a mixture of the tri and tetra components.

The following P-series glycol ethers (and acetates) have been included in the category of P-series glycol ethers. The listed CAS numbers are the ones used for the REACH registration of these substances. Both the IUPAC names (for the major isomer) and the common (public) names have been given for each of them.

One PO-unit

Mono-propylene glycol ethers + acetates				
Abbreviation	IUPAC name and common name	SMILES code	CAS no	Mol wt (g/mol)
PGME	1-methoxypropan-2-ol	COCC(C)O	107-98-2	90.1
	Propylene glycol methyl ether			
PGMEA	2-methoxy-1-methylethyl acetate	O=C(OC(C)COC)C	108-65-6	132.2
	Propylene glycol methyl ether acetate			
PGEE	1-ethoxypropan-2-ol	OC(C)COCC	1569-02-4	104.1
	Propylene glycol ethyl ether			
PGEEA	1-ethoxy-2-propanol acetate	O=C(OC(C)COCC)C	54839-24-6	146.2
	propylene glycol ethyl ether acetate			
PGnPE	1-propoxypropan-2-ol	OC(C)COCCC	1569-01-3	118.2
	Propylene glycol n-propyl ether			
PGBE	1-butoxypropan-2-ol	CCCCOCC(C)O	5131-66-8	132.2
	Propylene glycol butyl ether			

Two PO-units

Di-propylene glycol ethers + acetates				
Abbreviation	IUPAC name and public name	SMILES code	CAS no	Mol wt (g/mol)
DPGME	(2-methoxymethylethoxy)-1-propanol	OCC(OCC(OC)C)C	34590-94-8	148.2
	Dipropylene glycol methyl ether			
DPGMEA	Propanol, 1(or 2)-(2-methoxy-methylethoxy)-acetate	O=C(OC(OCCCCOC)CC)C	88917-22-0	190.2
	Dipropylene glycol methyl ether acetate			
DPGEE	(2-Ethoxymethylethoxy)propanol	CCC(O)OCCCCOCC	30025-38-8	162.0
	Dipropylene glycol ethyl ether			
DPGnPE	1-(1-methyl-2-propoxyethoxy)-propan-2-ol	O(CCC)CCCCOCCCO	29911-27-1	176.3
	Dipropylene glycol propyl ether			
DPGBE	1-(2-butoxy-1-methylethoxy)-propan-2-ol	O(CCCC)CC(OCC(O)C)C	29911-28-2	190.3
	Dipropylene glycol butyl ether			

Three PO-units

Tri-propylene glycol ethers				
Abbreviation	IUPAC name and public name	SMILES code	CAS no	Mol wt (g/mol)
TPGME	2-[2-(2-methoxy-1-methylethoxy)-1-methylethoxy]propan-1-ol	<chem>O(C(C)CO)CC(OCC(OC)C)C</chem>	25498-49-1	206.3
	Tripropylene glycol methyl ether			
TPGBE	1-[2-(2-butoxy-1-methylethoxy)-1-methylethoxy]propan-1-ol	<chem>OC(CC)OC(C)COC(C)COCCCC</chem>	55934-93-5	248.4
	Tripropylene glycol butyl ether			

Four or more PO-units

Polypropylene glycol ethers				
Abbreviation	IUPAC name and public name	SMILES code	CAS no	Mol wt (g/mol)
TPGBE - highers	Poly[oxy(methyl-1,2-ethanediyl)], α -butyl- ω -hydroxy-	not available	9003-13-8	
	Tripropylene glycol butyl ether highers			

1.4 Purity/impurities

The propylene glycol mono-alkyl ethers and their acetates are generally >95% pure, with typical purities of >99.5% (α -isomer). The corresponding β -isomer is the major impurity in these glycol ethers.

The di-propylene and tri-propylene glycol alkyl ethers contain 4 and 8 isomers (RR and RS enantiomers), respectively. The tri-propylene glycol alkyl ethers can contain small amounts of the lower members of the family as well. Individual isomers of these glycol ethers do not exist commercially; the products on the market are – for the purpose of REACH - considered as reaction masses. They have been tested for their hazardous properties with all isomers present.

The ‘heavy’ glycol ether streams are not supplied in pure form. They can contain mixtures of predominantly tri and tetra members but also significant amounts of penta, hexa, hepta molecules (containing 5, 6 and 7 PO units respectively). The commercial product TetraPGBE-highers also contains between 0.1 and 2% of KOH (typical value 0.2%). This is important when discussing the irritation endpoint of this product.

1.5 Classification and labelling

The comprehensive dataset for the P-Series glycol ethers does not support classification for significant human health hazards, i.e. CMR endpoints or sensitisation. When classified, the classification is limited to flammability, skin- and/or eye irritation and CNS depression (drowsiness/dizziness). None of the P-series glycol ethers are classified for environmental hazards.

Substance	CAS No.	Classification (EU DSD or *self-classific.)	EU-CLP (GHS)
PGME	107-98-2	R10, R67	Flam Liq 3, H226: STOT SE3, H336
PGMEA	108-65-6	R10	Flam Liq 3, H226
PGEE	1569-02-4	R10, R67	Flam Liq 3, H226; STOT SE3, H336; Eye Irrit 2, H319
PGEEA	54839-24-6	R10, R67	Flam Liq 3, H226; STOT SE3, H336
PGnPE	1569-01-3	R10*	Flam Liq 3, H226; Eye Irrit 2, H319
PBGE	5131-66-8	Xi; R36/38	Skin Irrit 2, H315; Eye Irrit 2, H319
DPGME	34590-94-8	not classified	
DPGMEA	88917-22-0	not classified	
DPGEE	30025-38-8	not classified	
DPGnPE	29911-27-1	not classified	
DPGBE	29911-28-2	not classified	
TPGME	25498-49-1	not classified	
TPGBE	55934-93-5	not classified	
TPGBE - highers	9003-13-8	Xn: R22, Xi: R36/38*	Acute Tox 4, H302; Skin Irrit 2, H315; Eye Irrit 2, H319

2. Absorption, Distribution and Metabolism

2.1. Absorption and distribution

The P-series category of glycol ethers share common paths of absorption, distribution, metabolism and elimination. ADME data are available on several members of the P-series glycol ethers category

Oral

Within the group of P-series glycol ethers, in vivo ADME data are available for propylene glycol methyl ether (PM), propylene glycol methyl ether acetate (PMA), dipropylene glycol methyl ether (DPM), tripropylene glycol methyl ether (TPM) and Dipropylene glycol butyl ether (DPnB). The data demonstrate that these substances are all well absorbed via the oral route with close to 100% of the administered dose available systemically.

Inhalation

No data are available from inhalation toxicokinetic studies, however given that the P-series glycol ethers are all highly water soluble liquids, have molecular weights between 100 and 300 Dalton and Log Pow values in the range of approximately 0 to 2, it is expected that they will be effectively absorbed via the inhalation route. However it should be recognised that as molecular weight increases, the volatility decreases, limiting the potential for significant inhalation exposure.

Dermal

Dermal penetration studies are available for PM, DPM and Dipropylene glycol n-propyl ether (DPnP). The data show that substances were able to penetrate (to some extent) human skin in vitro (PM and DPM), rat skin (PM) and rabbit skin in vivo (DPnP). Comparing the human data for PM to DPM, the dermal penetration rate for PM was 1.17 mg/cm²/h and for DPM 0.228 mg/cm²/h, indicating that as the number of PO units increases, the potential to penetrate the skin decreased significantly. Based on comparison with other similar substances, the EU risk assessment for PM concluded that it is approximately 30% bioavailable via the dermal route. Comparing the penetration rates of PM and DPM, it is reasonable to predict that the bioavailability of DPM would be lower, and unlikely to be more than 10-20%. This is consistent with the data for DPnP, where dermal bioavailability in vivo (in rabbits) following a single exposure for 6 hours was approximately 20%. According to the 2004 guidance from the European Commission on Dermal penetration, dermal absorption of chemicals can vary significantly between animals. Specifically, it is reported that rabbits and rats typically have a far greater permeability (between 2 and 10 fold difference) relative to humans. Based on this it is reasonable to assume that the degree of dermal penetration of DPnP in humans would be lower than in rabbits by at least a factor of 2, i.e. closer to 10%. So for the purposes of risk characterisation, it is assumed that human dermal bioavailability of the mono propylene glycol ethers (PM, PE, PnP)

and PnB) would be approximately 30%; the Dipropylene glycol ethers (DPM, DPE, DPnP and DPnB) would be between 10 and 20%; a conservative 20% will be used. There are no dermal penetration data available for the tripropylene glycol ethers (TPM and TPnB), or the Tetrapropylene glycol butyl ether Highers (TPnB-highers). Based on the data from the mono and Dipropylene glycol ethers a conservative estimate of 20% dermal bioavailability is taken.

With regards to the glycol ether acetates (PMA, DPMA, and PGEA), in an in vivo study comparing systemic availability of PM and PMA following a dermal exposure of rats (2 dose levels, ca. 130 and 1000 mg/kg bw), it was apparent that the bioavailability of PMA was no more than 1/3rd of that for PM. As such, the dermal bioavailability of the acetates is predicted to be approximately 1/3rd of the corresponding glycol ether, i.e. PMA and PEA are approximately 10% and DPMA is approximately 6%.

Once the P-series glycol ethers become systemically available, their high level of water solubility and low Log Pow values will mean that they have a tendency to move with the body water, i.e. will have a volume of distribution close to 1. They will not bioaccumulate in any tissues, and this is supported by the available ADME data on the group that demonstrate their rapid removal from the body and absence of accumulation in any tissue.

2.2. Metabolism

The available data on metabolism shows that these substances generally share the same overall metabolic pathway, with similar metabolites being produced. This provides the support to the overarching hypothesis that they will all have similar toxicological properties.

However, there are some differences in toxicity between the α -isomer and the β -isomer (impurity) of PGME, which are related to differences in their metabolism. The main difference between these 2 isomers is the location of the alcohol group – primary or secondary. Where this alcohol is a primary alcohol, metabolism can occur via alcohol dehydrogenase (ADH) to the corresponding acid (see Figure 1), in addition to the metabolism of the ether bonds and conjugation pathway.

The toxicity of the propylene glycol ethers with the alkoxy group at the primary position (α -isomer, which is the main isomer found in commercial products) is quite different from that of the ethylene glycol ethers. None of the reproductive effects as observed with the lower molecular weight ethylene glycol ethers have been reported for propylene glycol ethers in commerce, and the only evidence of toxicity is towards liver and kidney.

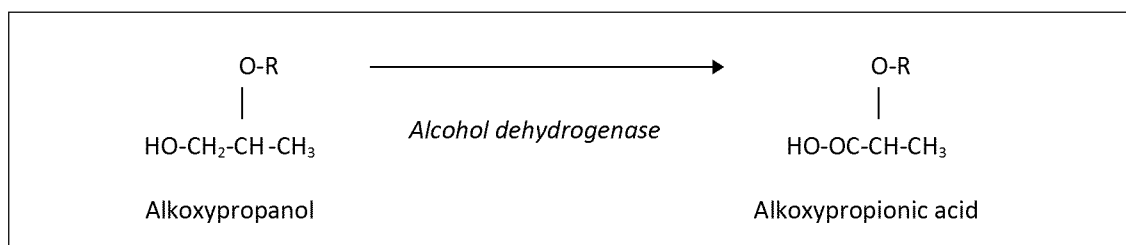
Mono-propylene glycol ethers

Mono-propylene glycol mono-alkyl ethers etherified at the primary carbon (*sec*-alkoxypropanols), like the α -isomer of PGME, are secondary alcohols that cannot be metabolised to alkoxypropionic acids (Figure 2). These compounds are either renally excreted after conjugation with sulphate, glucuronic acid or glycine or, to some extent may form ketones that may enter the intermediary metabolism via the TCA cycle, eventually to CO₂.

Mono-propylene glycol mono-alkyl ethers etherified at the secondary carbon (*n*-alkoxypropanols), like the β -isomer of PGME, are primary alcohols that can be oxidised via

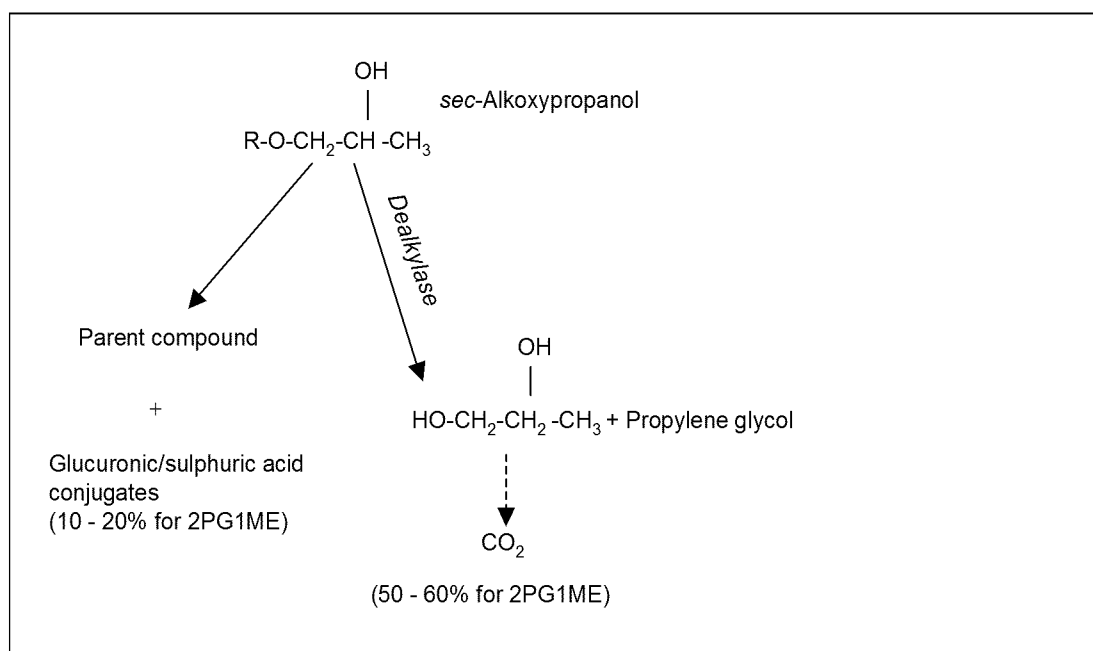
ADH to their corresponding alkoxypropionic acids (Figure 2). Thus, for example, the β -isomer of PGME and its acetate are oxidised to 2-MPA. It is presumed that 2-MPA is the teratogenic metabolite derived from β - PGME, which is a very minor impurity in commercial PGME.

Figure 1: Initial metabolic pathways of propylene glycol ethers with secondary ether bond ^a
(from ECETOC report on Glycol Ethers, 2005)



^a Primary alcohol (β -isomer)

Figure 2: Metabolic pathways of propylene glycol mono-alkyl ethers with primary ether bond ^a
(from ECETOC report on Glycol Ethers, 2005)



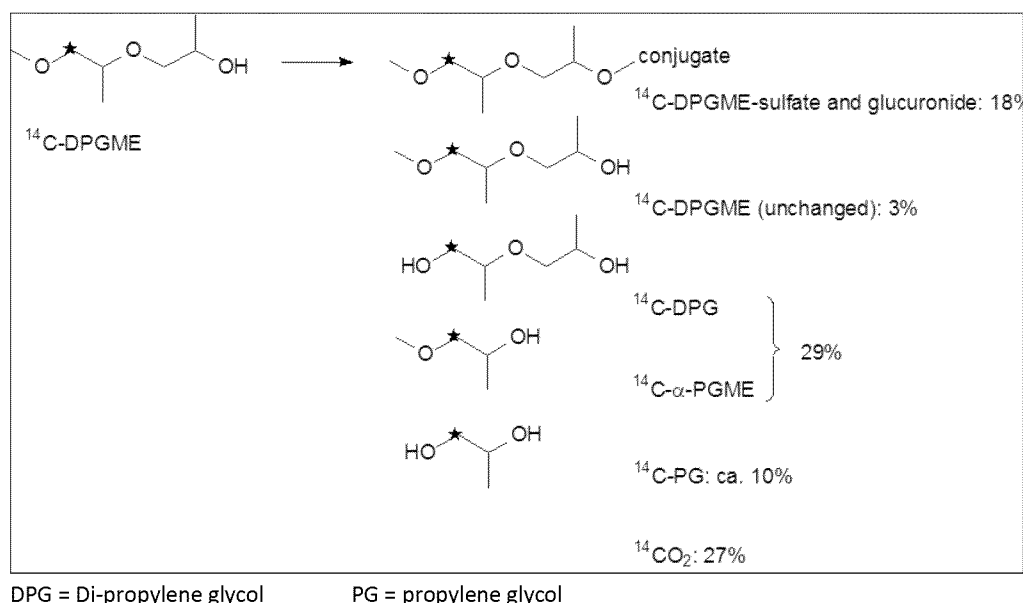
^a Secondary alcohols (α -isomer)

Di- and tri-propylene glycol ethers

Commercial di- and tri-propylene glycol ethers (DPGME, TPGME) contain four or more isomers. A small percentage (< 5%) of each substance might comprise isomers with a terminal hydroxyl group. These isomers are theoretical substrates for ADH, either directly or after O-dealkylation of DPGME or TPGME. The metabolic studies carried out with these substances have identified a

small amount of 2-MPA in rats. However, the main metabolic route for these glycol ethers is via dealkylation. The parent compound, DPGME, dipropylene glycol and the sulphates and glucuronides of DPGME have been identified as the main urinary metabolites (Calhoun *et al*, 1986a,b; Miller, 1987).

Figure 3: Metabolic pathways of di-propylene glycol methyl ether (according to Miller *et al*, 1985)



Glycol ether acetates

The glycol ether acetates are widely viewed as being rapidly hydrolysed to the glycol ether and acetic acid *in vivo* (Gargas *et al*. 2000; Corley *et al*. 2005; Louisse *et al*. 2010) due to the ubiquitous presence of carboxylesterases that hydrolyse the glycol ether acetates throughout the body. This is consistent with the view that the metabolism of the glycol ether acetates is similar to that of the parent glycol ether and that, therefore, their toxicity profile is mostly comparable with that of the parent glycol ether.

Data are available for the acetate esters of some E-series glycol ethers (EGME, EGEE, EGBE and DEGBE). They show rapid *in vitro* hydrolysis with half-lives varying from 1 to 12 minutes (OECD-SIAR No. 17, 2003). For some of the E-series glycol ethers acetates (EGEEA and DEGBEA), *in vivo* metabolism data are available, which show that they are rapidly metabolised via carboxylesterases that are present in various tissues (Gargas *et al*, 2000; Deisinger and Guest, 1989).

For the P-series, kinetic studies of the propylene glycol mono-methyl ether acetate were carried out and published with the purpose of bridging systemic equivalency to PGME in order to support the use of the extensive PGME toxicity database for the acetate. The studies determined the rate of hydrolysis as well as the systemic kinetic equivalency of the acetate to the parent glycol ether.

In vitro assay systems have been used to determine, a) the rates of hydrolysis of propylene glycol

monomethyl ether acetate (PGMEA) in blood and liver samples homogenates of humans and rats (Domoradzki et al. 2003), and b) tissue partition coefficients. Hydrolysis rate was measured at dose levels of 5 and 50 µg/ml. In blood PGMEA hydrolysed to PGME quicker in the rat than human. Half-lives in blood were approximately 35 min for human and approximately 15 min for the rat. Liver hydrolysis of PGMEA to PGME did not differ between rat and human with a half-life of approximately 30 min. *In vivo* hydrolysis of the acetate ester bond was very rapid with an approximate half-life of 1.5 min for the low dose and 3.5 min for the high dose. Furthermore, once PGMEA hydrolyzed, the kinetics for the PGME, whether derived from the parent or generated from the acetate, were essentially equivalent, suggesting the PGME toxicological database can serve as a surrogate for the acetate to predict systemic effects of PGMEA with a high degree of confidence.

Glycol Ether Acetate	CAS Nr.	Half- life time for <i>in vitro</i> hydrolysis in rat blood plasma	Half- life time for <i>in vitro</i> hydrolysis in human blood plasma	<i>In vivo</i> hydrolysis in rats
EGMEA ¹	110-49-6	400 µg/ml: 11.75 min	not available	not available
EGEEA ¹	111-15-9	400 µg/ml: 9.92 min	not available	50 ppm inhalation: T _{1/2} < 1.0 min ²
EGBEA ¹	112-07-2	400 µg/ml: 0.96 min	not available	not available
DEGBEA ³	124-17-4	1021 µg/ml: < 3 min	not available	rapid metabolism <i>in vivo</i> ³
PGMEA ⁴	108-65-6	5 µg/ml: 16 min 50 µg/ml: 15 min	5 µg/ml: 36 min 50 µg/ml: 34 min	14.7 mg/ml: 1.6 min 147 mg/ml: 2.3 min
DPGMEA ⁵	88917-22-0	7 µg/ml: 10.4-13.22 min 72 µg/ml: 12.09-16.89 min	not available	not available
PGEEA ⁶	54839-24-6	35.5 µg/ml: 48 min 355 µg/ml: 48 min	not available	not available

¹ data from an unpublished report by BASF ²data from Gargas et al (2000) ³data from Deisinger and Guest (1989)

⁴ data from Domoradzki et al (2003) ⁵data from Saghir et al (2012) ⁶data from INEOS Oxide (2012)

These *in vitro* derived estimates of hydrolysis and tissue partitioning have been successfully scaled to predict *in vivo* kinetics of PGMEA and PGME in rats and humans using a physiologically based pharmacokinetic (PBPK) model (Corley et al. 2005).

Estimates of *in vitro* hydrolysis of DPGMEA and tissue partition coefficients have been determined (Saghir et al., 2012) in rat blood and liver samples. Furthermore, model simulations have been used to predict *in vivo* kinetics of DPGME and its acetate DPGMEA in rats, following a single gavage dose using estimates of hydrolysis and partitioning derived from *in vitro* assays.

The results of these model simulations suggest that, despite having slower rates of hydrolysis in liver, DPGMA does not accumulate in tissue any more than PGMEA does. The reasons for this are two-fold.

- The results of the PBPK model simulations show that the rate of hydrolysis of the acetate *in vivo* is dominated by the capacity of the blood to hydrolyse PGMEA and DPGMEA.
- DPGMEA has tissue partition coefficients that are less than 2.0, indicating no particular

preference for DPGMEA to sequester in any specific tissue. In addition, the glycol ethers and their acetates have been shown to not be diffusion limited (Corley et al., 2005; Gargas et al., 2000).

This means that the glycol ethers and their acetates freely and rapidly distribute to tissues and back to the blood stream. Therefore, as the glycol ether acetate is rapidly hydrolysed in the blood, the concentration gradient favours the glycol ether acetate to partition back into the blood stream, thereby making the systemic tissue concentration of the glycol ether acetate to mirror that of the concentration in blood.

These two factors work together to make it such that glycol ether acetates have short half-lives in the blood and systemic tissues, even when a particular glycol ether acetate has a substantially lower rate of hydrolysis in any particular tissue.

It has also been shown through the use of the PBPK model (Appendix 2) that the AUC estimates for DPGME are essentially identical whether exposure is to DPGME or DPGMEA (same results were shown for PGMEA and PGME). In addition, the Area under the Curve (AUC) for DPGMEA *in vivo* is extremely low compared to the AUC for DPGME. The simulations from the PBPK model suggest following an oral dose, that; a) DPGMEA will have a very short half-life in blood and a very low AUC in blood and tissues, b) there will be no tissue sequestration, despite lower hydrolysis rates in liver tissues, and c) the AUC for DGPME will be essentially identical (less than 1% difference) following either a DPGME or DPGMEA oral dose, it can be assumed that the systemic toxicity of DPGMEA is very likely to be identical to DPGME following oral exposures.

In conclusion, the metabolism of the acetates to the glycol ether is well understood and supported by the available data, therefore read across from the ether to the respective acetate is considered justified.

3. Data matrix for Glycol Ether P-series Category

3.1 Physicochemical Properties

With exemption of the dissociation constant, which is not considered to be relevant for the P-series glycol ethers, the members of the category have a rich database for physicochemical endpoints. No significant data gaps have been observed.

Melting point

Melting points are available for all members of the P-series category of glycol ethers and are, with only a few exemptions, almost constant across and down the category. All category members are liquids at room temperature.

PROPERTY:	MELTING POINT (Celsius)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	-96	-70	-70	-80
Di	-83	-50	-85	-75
Tri	-78			-75
Tetra (highers)				-20
Mono-acetate	-66	-89		
Di-acetate	-25			

Boiling point

Boiling point values are available for all members of the P-series category of glycol ethers. There is a clear trend across and down the category: boiling points increase with increasing length of the alcohol moiety and the number of PO-units in the molecule.

PROPERTY:	BOILING POINT (Celsius)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	120	132	149	171
Di	190	188	212	230
Tri	243			276
Tetra (highers)				306
Mono-acetate	146	158		
Di-acetate	209			

Density

Density values are available for all members of the P-series category of glycol ethers and are almost constant across and down the category.

PROPERTY:	DENSITY (kg/m ³)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	921	897	885	880
Di	954	942	921	913
Tri	965			924
Tetra (highers)				949
Mono-acetate	967	941		
Di-acetate	976			

Vapour pressure

Values for vapour pressure are available for all members of the P-series category of glycol ethers. There is a clear trend in vapour pressure across and down the category: the vapour pressure decreases with increasing length of the alcohol moiety and with increasing number of PO-units in the molecules.

PROPERTY:	VAPOUR PRESSURE (Pa)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	1560	1000	380	139
Di	37	56.7	10	4
Tri	1.7			0.2
Tetra (highers)				0.076
Mono-acetate	502	202		
Di-acetate	10.4			

Partition coefficient

Partition coefficients are available for all members of the category. For one member the value has been estimated by QSAR. There does not seem to be a clear trend, but for the propyl- and butyl derivatives, the log Kow seems to increase slightly with the number of PO-units in the molecules. Generally, the log Kow values for P-series glycol ethers are low which indicate that they would not be expected to bioaccumulate in the environment.

PROPERTY:	PARTITION COEFFICIENT (log Kow)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	0.37	0.0 ¹	0.62	1.2
Di	0.0043	0.16	0.89	1.52
Tri	0.31			1.9
Tetra (highers)				1.18-4.37 ²
Mono-acetate	1.2	0.76		
Di-acetate	0.61			

¹ QSAR ² Range based on the peaks observed in the HPLC chromatogram.

Water solubility

Most members of the P-series category of glycol ethers are full miscible with water, with the exemption of the butyl derivatives which show a water solubility of 4 to 6%. The acetates are generally less water soluble than the parent glycol ethers.

PROPERTY:	WATER SOLUBILITY (g/l)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	fully miscible	fully miscible ¹	fully miscible	55
Di	fully miscible	fully miscible	150	40
Tri	fully miscible			40
Tetra (highers)				42
Mono-acetate	198	69.6		
Di-acetate	183			

¹ Calculated value 366 g/l

Surface tension

For most members of the category surface tension values are available. There is not a clear trend in surface tension with the number of PO units in the molecule. The surface tension values are more or less the same down the category with exemption of the acetate of the propylene glycol methyl ether. With increasing length of the alcohol moiety the surface tension seems to decrease at least for the mono-alkoxy glycol ethers.

PROPERTY:	SURFACE TENSION (mN/m)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	70.7	57.7 ¹	n.a.	27.6
Di	68.7	n.a.	64.6	n.a.
Tri	68.8			n.a.
Tetra (highers)				44.6
Mono-acetate	29.4	39.1 ²		
Di-acetate	54.2			

n.a. = no data available

¹ The surface tension of PGEE has not been measured at the preferred concentration of 1000 mg/l. However, measured data available down to a dilution of 20% can be extrapolated to predict a surface tension of around 57mN/m at a solution strength of around 5% with reasonable accuracy.

² measured with a saturated solution

Flash point

With exemption of the acetate of propylene glycol ethyl ether, flash points are available for all members of the category. There is a clear increase in flash point with increasing length of the alcohol moiety and with the number of PO-units in the molecules. The glycol ethers with a flash point below 60 °C are classified as flammable.

PROPERTY:	FLASH POINT (Celsius)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	31 ¹	40 ¹	46 ¹	63
Di	75	82	94	101
Tri	124			126
Tetra (highers)				202
Mono-acetate	46 ¹	n.a.		
Di-acetate	87			

¹ classified as flammable n.a. = no data

Auto-ignition temperature

Auto-ignition temperatures are available for all members of the P-series category of glycol ethers. All values around 200 °C or higher without a clear trend across and down the category.

PROPERTY:	AUTOIGNITION TEMPERATURE (Celsius)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	287	255 ¹	252	260
Di	207	199	205	194
Tri	277			202
Tetra (highers)				350

Mono-acetate	333	325		
Di-acetate	340			

¹ Value from Handbook

Dissociation constant

Dissociation constants are not relevant for this type of substances. Examination of the chemical structure of propylene glycol ethers shows that there is no functional group that could dissociate. The substances do not contain acidic or basic functional groups.

Viscosity

Viscosity values are available for all members of the category. There is a clear increase in viscosity with increasing length of the alcohol moiety and with the number of PO-units in the P-series glycol ethers. For the acetates, there is a clear trend that the acetate has a lower viscosity than the corresponding glycol ether.

PROPERTY:	VISCOSITY (mPa.s)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	1.90	2.21	2.80	3.85
Di	4.55	4.20	4.70	5.84
Tri	6.71			8.79
Tetra (highers)				19.0
Mono-acetate	1.23	1.33		
Di-acetate	2.52			

3.2 Environmental Fate

Photo-degradation

Information on photo-degradation in air is available for 8 out the 14 category members. The available data support the conclusion that all category members will rapidly decompose in the atmosphere under the influence of light (i.e. half-lives less than a day).

PROPERTY:	PHOTODEGRADATION (BY QSAR) – HALF LIFE (HRS)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	3.1	5.9 ¹	n.a.	n.a.
Di	n.a.	n.a.	n.a.	7.2
Tri	4.1 ¹			1.9
Tetra (highers)				0.1
Mono-acetate	n.a.	7.5 ¹		
Di-acetate	3.8 ¹			

¹EPIWIN or AOPWIN calculation

n.a. = no data available

Biodegradability

All members of the category have biodegradation data available. With the exception of dipropylene glycol methyl ether acetate (DPGMEA), all category members are readily biodegradable. Di-propylene glycol methyl ether acetate (DPGMEA) was not readily biodegradable in three tests for ready biodegradation. However, primary degradation of the acetate to the corresponding di-propylene glycol methyl ether (DPGME) was observed in the MITI test. Once DPGME is formed, full mineralisation can be expected as this glycol ether has been shown to be readily biodegradable in the OECD 301F Manometric Respirometry test. The test methodology used does not allow the conclusion that DPGMEA is “readily degradable. DPGMEA can be classified as “inherently biodegradable fulfilling the criteria”. These biodegradation data support the conclusion that category members would not be persistent in the environment.

PROPERTY:	AEROBIC BIODEGRADATION SCREENING RESULTS			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	RB	RB	RB	RB
Di	RB	RB	RB	RB
Tri	RB			RB
Tetra (highers)				RB
Mono-acetate	RB	RB		
Di-acetate	IB ¹			

RB = readily biodegradable. IB = inherently biodegradable

¹ not readily biodegradable in the closed bottle test, in a BOD test and in a MITI test

3.3 Environmental Toxicity

For the P-series glycol ethers, there is no real discernible trend in ecotoxicity. However, where measured data are available the P-series glycol ethers demonstrate a low order of toxicity with LC₅₀ or EC₅₀ values in excess of the limit dose. Therefore, where experimental data are not available it is predicted that there is no toxicity at a concentration lower than the limit dose.

For the acetates, it appears that they are typically more toxic than the parent glycol ethers; however they still demonstrate a low order of toxicity.

Acute toxicity – fish

Most members of the category have acute fish toxicity data available. All LC₅₀ values are clearly above 100 mg/l, which indicates that the P-series glycol ethers are not acutely toxic to fish.

PROPERTY:	FISH LC ₅₀ (mg/l)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	6812	n.a. ¹	>100	>560
Di	>1000	>200	>100	841
Tri	11619			564
Tetra (highers)				n.a. ²
Mono-acetate	134	140		
Di-acetate	111			

n.a. = no data available

¹ In the REACH dossier, read-across was used from DPGEE: QSAR indicates LC₅₀ value of 4598 mg/l

² In the REACH dossier, read-across was used from TPGBE

Acute toxicity – aquatic invertebrates

For most members of the category acute toxicity data for aquatic invertebrates (Daphnia) are available. All LC₅₀ values are clearly above 100 mg/l, which indicates that the P-series glycol ethers are not acutely toxic to aquatic invertebrates.

PROPERTY:	INVERTEBRATES EC ₅₀ (mg/l)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	23300	n.a. ¹	>100	>1000
Di	1919	>150 ²	>100	>1000
Tri	>10000			>1000
Tetra (highers)				n.a. ³
Mono-acetate	408	110		
Di-acetate	1090			

n.a. = no data available

¹ EC₅₀ estimated to be >100 mg/l based on data from DPGEE (read-across).

QSAR indicates a 48-h EC₅₀ of 1929 mg/l.

² Experimental result. QSAR estimate: 2297mg/l.

³ In the REACH dossier, read-across was used from TPGBE

Acute toxicity – aquatic plants

For all members of the category acute toxicity for algae data are available. All EC₅₀ values are clearly above 100 mg/l, which indicates that the P-series glycol ethers are not acutely toxic to aquatic plants.

PROPERTY:	ALGAE EC ₅₀ (mg/l)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	>1000	>100	3440	>1000
Di	>969	>100	>1000	519
Tri	21010			592
Tetra (highers)				333
Mono-acetate	>1000	>100		
Di-acetate	>1000			

Acute toxicity – aquatic microorganisms

For most members of the category, acute toxicity data for micro-organisms are available. With the exception of propylene glycol propyl ether, all EC₅₀ values are clearly above 100 mg/l, which indicates that the P-series glycol ethers are not acutely toxic to micro-organisms.

PROPERTY:	MICRO-ORGANISMS EC ₅₀ (mg/l)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	>1000	4600 ¹	40	>1000
Di	>4168	n.a.	n.a.	>1000
Tri	>2000			>1000
Tetra (highers)				>1000
Mono-acetate	>1000	560 ¹		
Di-acetate	>1000 ¹			

¹ EC₁₀ after a 16-h exposure (static) to *Pseudomonas putida*

n.a. = no data available

Chronic toxicity – fish

Chronic toxicity data for fish are available for some members of the category. Where data are available, they demonstrate a low order of toxicity. Due to the biodegradability, low Log Kow and the low order of acute ecotoxicity across the category no additional testing (to meet the requirements of Annex IX and X of the REACH text) has been triggered. Therefore further chronic or reproductive toxicity testing in fish has been waived.

PROPERTY:	FISH NOEC (mg/l)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	n.a.	n.a. ¹	n.a.	n.a.
Di	n.a.	>200	n.a.	n.a.
Tri	n.a.			n.a.
Tetra (highers)				n.a.
Mono-acetate	47.5	n.a. ²		
Di-acetate	n.a.			

¹ Read-across from DPGE and based on model estimates

² In REACH dossier, read-across from PGMEA was used (NOEC = 53 mg/l)

n.a. = no data available

Chronic toxicity – aquatic invertebrates

Chronic toxicity data for aquatic invertebrates are available for some members of the category. Where data are available, they demonstrate a low order of toxicity. Due to the biodegradability, low Log Kow and the low order of acute ecotoxicity across the category, no additional testing (to meet the requirements of Annex IX and X of the REACH text) has been triggered. Therefore further chronic toxicity tests with aquatic invertebrates could be waived according to the REACH regulation.

PROPERTY:	INVERTEBRATES NOEC (mg/l)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	n.a.	>100 ¹	n.a.	n.a.
Di	>0.5	>180	n.a.	n.a.
Tri	n.a.			n.a.
Tetra (highers)				n.a.
Mono-acetate	100	n.a. ²		
Di-acetate	n.a.			

¹ Read-across from DPGE and based on model estimates

² In REACH dossier, read-across from PGMEA was used (NOEC > 100 mg/l)

n.a. = no data available

Chronic toxicity – aquatic plants

Chronic toxicity data for algae are available for some members of the category. Where data are available, they demonstrate a low order of toxicity. Due to the biodegradability, low Log Kow and the low order of acute ecotoxicity across the category no additional testing (to meet the requirements of Annex IX and X of the REACH text) has been triggered. Therefore further chronic toxicity tests with algae could be waived according to the REACH regulation.

PROPERTY:	ALGAE NOEC (mg/l)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	n.a.	> 100	n.a.	560
Di	n.a.	> 100	125	n.a.
Tri	n.a. ¹			253
Tetra (highers)				94
Mono-acetate	n.a.	≥ 100		
Di-acetate	n.a.			

¹ Study available with *Lemna minor* (duck weed): NOEC = 482.5 mg/ml

n.a. = no data available

3.4 Mammalian Toxicity

Acute toxicity

For the P-series glycol ethers, there is no real discernible trend in acute toxicity. However, where measured data are available the P-series glycol ethers demonstrate a low order of toxicity with LD₅₀ or LC₅₀ values in excess of the limit dose. The only exception is the tetra-highers (see below). For the acetates, there is no evidence that they are more toxic than the parent glycol ethers; they demonstrate a low order of toxicity.

Acute toxicity – oral

The acute toxicity via the oral route has been well studied for all category members with data available for each member and in some cases using several different species (mice, rat, and rabbit). The data demonstrate that the category members have a low order of acute oral toxicity with LD₅₀ values for almost all members >2000 mg/kg bw. The exceptions are propylene glycol ethyl ether (PGEE) and the Tetra-highers. In the LD₅₀ study with PGEE the highest dose tested was 2 ml/kg, which is equivalent to 1792 mg/kg based on the density. However there was no evidence of mortality at this dose and the LD₅₀ values of the methyl, propyl and butyl ethers suggest that the LD₅₀ value would be >2000 mg/kg. The tetra-highers is the only category member that is classified for acute toxicity (category 4). It is unclear why the acute toxicity is greater for this substance.

PROPERTY:	ORAL LD ₅₀ (mg/kg) – RAT			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	4016	>1792 ¹	>2000	3300
Di	>5000	>4700	>2000	>2000
Tri	3400			2600
Tetra (highers)				>300 - <2000
Mono-acetate	>5000	>4700		
Di-acetate	>5000			

¹ highest dose used (2 ml/kg bw): no deaths observed

Acute toxicity – inhalation

For most members of the P-series category, the inhalation route is an appropriate route of exposure. The ability to test high concentrations of the glycol ethers by the inhalation route is limited by their vapour pressure. The di-, tri- and higher propylene glycol ethers typically have a relatively low volatility. With increasing length of the alcohol moiety in the molecule and increasing number of PO units, the LC₅₀ values decrease and thus the toxicity seem to increase. However, in many cases the acute inhalation toxicity studies have been conducted at the highest attainable/saturated vapour concentration at which no signs of toxicity have been observed. Although for many members of the category, the reported LC₅₀ values are below the classification

limit of 20 mg/l, these glycol ethers do not meet the criteria for classification as “harmful by inhalation” as no mortality has been observed at the maximum achievable vapour concentrations.

PROPERTY:	INHALATION LC ₅₀ (mg/m ³) – RAT			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	25796	>9590 ¹	>8340 ¹	>3515 ¹
Di	>3350 ¹	>2410 ¹	n.a. ³	>2040 ²
Tri	>253 ¹			n.a. ³
Tetra (highers)				n.a. ³
Mono-acetate	>10800 ¹	>6900 ¹		
Di-acetate	>5700 ¹			

¹ Highest attainable/saturated vapour concentration

² Aerosol concentration

³ n.a. = no data available due to very low vapour pressure

Acute toxicity – dermal

All, but two members of the category have acute dermal toxicity data. All LD₅₀ values are above 2000 mg/kg bw, which means that, similarly to the oral route, these glycol ethers demonstrate a low order of toxicity and do not need to be classified for acute toxicity properties via the dermal route.

PROPERTY:	DERMAL LD ₅₀ (mg/kg) Rabbit			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	>2000	n.a. ¹	>2000	>2000
Di	>9510	>2000	>2000	>2000
Tri	15440			>2000
Tetra (highers)				>2000
Mono-acetate	>5000	n.a. ¹		
Di-acetate	>2000			

¹ Read-across from PGME used in the REACH dossier

n.a. = no data available

Skin irritation

With exemption of the mono-propylene glycol butyl ether and the butyl “heavies”, none of the P-series glycol ethers is classified for skin irritation properties. There seems to be a slight trend that skin irritation properties increase with increase of the alcohol chain length.

PROPERTY:	SKIN IRRITATION			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	no	no	no	yes
Di	no	no	no	no
Tri	no			no
Tetra (highers)				yes – equivocal ¹
Mono-acetate	no	no		
Di-acetate	no			

¹ No *in vivo* skin irritation test is available for the tetra-highers. This substance has been classified as a skin irritant due to residual alkalinity (potassium hydroxide) and pH >11.5. In the past the commercial product contained >0.5% potassium hydroxide as an additive. When the KOH concentration in the product is < 0.5%, there is no need for classification.

Eye irritation

With exemption of the mono-propylene glycol ethyl, propyl and butyl ether and the butyl “heavies”, none of the P-series glycol ethers is classified for eye irritation properties. There seems to be a slight trend that eye irritation properties increase with increasing alcohol chain length.

PROPERTY:	EYE IRRITATION			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	no	yes	yes	yes
Di	no	no	no	no
Tri	no			no
Tetra (highers)				yes ¹
Mono-acetate	no	no		
Di-acetate	no			

¹ No *in vivo* eye irritation test is available for the tetra-highers. This substance has been classified as an eye irritant due to residual alkalinity (potassium hydroxide) and pH >11.5. In the past the commercial product contained >0.5% potassium hydroxide as an additive. When the KOH concentration in the product is < 0.5%, there is no need for classification.

Skin sensitisation

From various types of studies (GPMT, Buehler test, LLNA), there is clear evidence across the whole category that the P-series glycol ethers do not have skin sensitisation properties.

PROPERTY:	SKIN SENSITISATION
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Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	no	no ¹	no	no
Di	no	no	no	no
Tri	no			no
Tetra (highers)				no
Mono-acetate	no	no		
Di-acetate	no			

¹ Read-across from other P-series glycol ethers

Mutagenicity

There are sufficient data on the category members to support the conclusion that they are not genotoxic. In addition, there is no difference in genotoxicity between the acetates and their respective glycol ethers.

PROPERTY:	OVERALL EVIDENCE			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	no	no	no	no
Di	no	no	no	no ¹
Tri	no			no
Tetra (highers)				no
Mono-acetate	no	no		
Di-acetate	no			

¹ Ambiguous results in the chromosome aberration assay *in vitro*; negative in *in vivo* mouse micronucleus test

PROPERTY:	AVAILABLE TEST DATA			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	ACMI	ACM	ACM	ACM
Di	ACM	ACM	ACM	ACMI
Tri	ACMI			AMI
Tetra (highers)				ACM
Mono-acetate	ACMI	AC		
Di-acetate	ACM			

A=Ames, C=Cytogenicity, M= Mammalian cell gene mutation, I=in vivo

Repeated dose toxicity

The P-series glycol ethers have been extensively investigated for their repeat dose toxicity profile. Studies have been conducted in a variety of animal species, by different routes of exposure and

exposure durations. The ability to test by the inhalation route is limited by vapour pressure of the glycol ethers. The di-, tri- and higher propylene glycol ethers typically have a relatively low volatility. For these less volatile glycol ethers (e.g. the di- and tri-butyl derivatives), repeated dose toxicity studies are available via the dermal route.

Sub-acute studies

Sub-acute (up to 28-day) studies, either via the oral, inhalation or dermal route are available for some members of the P-series glycol ethers category. In some cases, the NOAELs of studies with a somewhat longer dosing period (e.g. OECD 422 study) have been included.

SUBSTANCE	SUB-ACUTE TOXICITY STUDIES		
	Oral (rats) NOAEL (mg/kg/day)	Inhalation (rats) NOAEC (mg/m ³)	Dermal (rabbits) NOAEL (mg/kg/day)
<i>Mono-alkoxy Glycol Ether</i>			
PGME	919 ¹	3700 ⁸	>1000
PGMEA	>1000 ²	1620 ⁹	>1000
PGEE	<1792 ³	1400 ¹⁰	n.a.
PGEEA	n.a. ⁴	7300	n.a.
PGnPE	n.a.	2500 ¹¹	n.a.
PGBE	n.a.	3244 ¹²	n.a.
<i>Di-alkoxy GE</i>			
DPGME	1000	2000	>1000
DPGMEA	1000	n.a.	n.a.
DPGEE	50 ⁵	n.a.	n.a.
DPGnPE	300 ⁶	n.a.	n.a.
DPGBE	>400 ⁶	>320 ¹³	n.a.
<i>Tri-alkoxy GE</i>			
TPGME	n.a.	1010 ¹³	n.a.
TPGBE	1000	n.a.	n.a.
TPGBE -highers	100 ⁷	n.a.	n.a.

n.a. = no data available

¹ NOAEL from a 35-day study in male rats

² NOAEL from an OECD 422 study

³ NOAEL from a 10-day study with 2 ml/kg/day

⁴ In the REACH dossier, read-across from 10-day study with PGEE was used

⁵ Male rat nephropathy at 225 and 1000 mg/kg bw (this was not observed in the 90-day study)

⁶ NOAEL from a 14-day study with daily exposure

⁷ NOAEL from an OECD 422 study

⁸ NOAEC (1000 ppm) from a 11-day inhalation study (9 exposures) in rats and mice

⁹ NOAEC (300 ppm) from a 11-day inhalation study (9 exposures) in rats

¹⁰ NOAEC (300 ppm) from a 11-day inhalation study (9 exposures) in rats

¹¹ NOAEC (500 ppm) from a 2-week inhalation study (10 exposures) in rats

¹² NOAEC (600 ppm) from a 31-day inhalation study in rats

¹³ NOAEC (max. attainable concentration) from a 2-week inhalation study (9 exposures) in rats

Sub-chronic studies

With the exception of the acetates and the butyl heavies, sub-chronic (90-day) toxicity studies

are available for all category members by at least one route of exposure. For some members, 90-day studies are available in both rats and rabbits. Ninety day studies via the inhalation route are only available for the mono-alkoxy glycol ethers and for di-propylene glycol methyl ether. For propylene glycol methyl ether, chronic (2-year) inhalation toxicity/carcinogenicity studies are available in rats and mice.

SUBSTANCE	SUB-CHRONIC (90-DAY) TOXICITY STUDIES		
<i>Mono-alkoxy Glycol Ether</i>	Oral (rats) NOAEL (mg/kg/day)	Inhalation (rats) NOAEC (mg/m ³)	Dermal (rabbits) NOAEL (mg/kg/day)
PGME	< 460 ¹	3740 ⁵ (rats and rabbits)	1840
PGMEA	n.a.	n.a. ⁶	n.a. ¹⁰
PGEE	n.a. ²	1266	n.a. ¹⁰
PGEEA	n.a. ³	n.a. ⁷	n.a. ¹⁰
PGnPE	n.a.	1448	n.a.
PGBE	350	3244	880
<i>Di-alkoxy GE</i>			
DPGME	n.a.	1212	2850
DPGMEA	n.a. ⁴	n.a. ⁸	n.a.
DPGEE	1000	n.a.	n.a.
DPGnPE	500	n.a.	n.a.
DPGBE	450	n.a.	91 ¹¹
<i>Tri-alkoxy GE</i>			
TPGME	n.a.	n.a. ⁹	965
TPGBE	1000	n.a.	n.a.
TPGBE -highers	n.a.	n.a.	n.a.

n.a. = no data available

¹ LOAEL = 460 mg/kg b.w.

² in the REACH dossier, read-across from sub-chronic studies with DPGEE was used.

³ in the REACH dossier, read-across from a sub-chronic study with PGEE was used.

⁴ in the REACH dossier, read-across from sub-chronic and chronic studies with PGME was used.

⁵ Same NOAEL (1000 ppm) was observed in a 90-day inhalation study in rabbits.

⁶ in the REACH dossier, read-across from a sub-chronic study with PGME was used.

⁷ in the REACH dossier, read-across from a sub-chronic study with PGEE was used.

⁸ in the REACH dossier read-across from a sub-chronic inhalation study with DPGME was used.

⁹ only a 2-week inhalation study with TPGME is available.

¹⁰ in the REACH dossier, read-across from the 90-day dermal study with PGME was used.

¹¹ The dermal repeated dose toxicity study with DPGBE was conducted in rats

In contrast to the effects observed with a number of ethylene glycol ethers, the propylene glycol ethers do not cause - even when tested at high dose levels – adverse effects on the haematopoietic system, reproductive organs or thymus. Target organs in repeated dose toxicity studies with P-series glycol ethers are mainly the liver (increased weight) and the kidney (increased weight and α_2 -globulin formation in male rats). Other effects observed are: mild transient sedation, reduced body weights, and local irritation of the skin or mucous membranes.

The results of the repeated dose toxicity studies indicate that these glycol ethers demonstrate a low order of toxicity and do not need to be classified for repeated dose toxicity properties via any exposure route. The available data for the category also demonstrate that increasing the alcohol chain length or increasing the PO units does not change the toxicity of the P-series glycol ethers significantly. The variation in NOAELs tend to vary by no more than a factor of ~2, except in the case of inhalation, where values are confounded by volatility limitations.

Where data are available (e.g. from sub-acute or reprotox screening studies), there is no evidence that the acetates are more toxic than the parent glycol ethers.

Developmental toxicity

For most members of the P-series glycol ethers category developmental toxicity studies are available, either via the oral, inhalation or dermal route. Data are available for each of the different alcohol groups – methyl, ethyl, propyl and butyl. For the methyl series, there are data for each of the mono-, di- and tri- glycol ethers. For some members of the category, studies are available for 2 routes of exposures. Some category members have been tested in 2 species (rats and rabbits). For four members of the category (PGEEA, DPGMEA, DPGEE and TPBGE), no specific developmental toxicity studies exist.

None of the category members tested produced developmental toxicity (i.e., no birth defects) by oral, inhalation, or dermal routes of exposure, even when tested at high doses. Some embryo- and/or fetotoxicity (post-implantation loss) was found where maternal toxicity existed. Increased incidences of variations/retardations (e.g., delayed skeletal ossification, increased incidence of 13th ribs) were sometime noted at high dose levels in conjunction with maternal toxicity (typically body weight reductions and reduced feed consumption).

Overall, the available data for the category demonstrate that increasing alcohol chain length does not increase toxicity, and increasing PO units does not increase toxicity. Where data exist in 2 species, it can be demonstrated that there are no significant differences in developmental toxicity between species.

Despite the favourable outcome of the developmental toxicity studies with P-series glycol ethers, questions have been raised because of the presence of various isomers in commercial P-series glycol ethers. Some of these isomers are primary alcohols and therefore have a similar structure as the E-series glycol ethers. One of the isomers that has been much debated is the β -isomer of propylene glycol methyl ether (β -PGME). Like other β -isomers, β -PGME is not a commercially available product as such, but is present in very small quantities (0.1-0.3%) in commercial PGME. A developmental toxicity study with β -PGME has shown skeletal anomalies in rats at 3000 ppm with minor variations at 1000 and 2000 ppm, and at 225 ppm and 350 ppm in rabbits. The NOEL for developmental toxicity in rabbits was 145 ppm, whereas maternal toxicity was observed at 545 ppm (Merkle *et al*, 1987; Hellwig, 1994).

Today, the commercially available mono-alkoxy propylene glycol ethers contain only a small amount of the β -isomer (see composition data in REACH dossier).

With regards to PGME and PGMEA, the developmental toxicity studies have been conducted with

test material containing up to 2% of the β -isomer, and – as mentioned above - did not cause any of the developmental effects.

SUBSTANCE	DEVELOPMENTAL TOXICITY STUDIES		
<i>Mono-alkoxy Glycol Ether</i>	Oral (rats) NOAEL (mg/kg/day)	Inhalation (rats) NOAEC (mg/m ³)	Dermal (rats or rabbits) NOAEL (mg/kg/day)
PGME	920	11058 ^{2,3} (rats and rabbits)	n.a.
PGMEA	1000 ¹	22464 ⁴	n.a.
PGEE	n.a.	8500 (rats) 5400 (rabbits)	n.a.
PGEEA	n.a.	n.a. ⁵	n.a.
PGnPE	n.a.	3626 ⁶ (rats and rabbits)	n.a.
PGBE	n.a.	n.a.	880 ⁹ (rats)
<i>Di-alkoxy GE</i>			
DPGME	n.a.	1818 ⁷ (rats and rabbits)	n.a.
DPGMEA	n.a.	n.a. ⁸	n.a.
DPGEE	n.a.	n.a. ⁵	n.a.
DPGnPE	n.a.	n.a.	1000 (rabbits)
DPGBE	1000 ¹	n.a.	910 ⁹ (rats)
<i>Tri-alkoxy GE</i>			
TPGME	n.a.	3000 (rabbits)	n.a.
TPGBE	n.a.	n.a.	n.a.
TPGBE -highers	500 ¹	n.a.	n.a.

n.a. = no data available

¹ NOAEL from an OECD 422 study

² Highest concentration tested (3000 ppm)

³ Same NOAEC observed in a inhalation developmental toxicity study with PGME in rabbits

⁴ NOAEC (4000 ppm) from a non-guideline study (of good quality) with PGMA (1989). In the REACH dossier, read-across from the developmental toxicity study with PGME was used ("Klimisch 1").

⁵ In the REACH dossier read-across from the developmental toxicity study with PGEE was used

⁶ Same NOAEC observed in a inhalation developmental toxicity study with PGnPE in rabbits

⁷ Same NOAEC (300 ppm) observed in a inhalation developmental toxicity study with DPGME in rabbits

⁸ In the REACH dossier read-across from the developmental toxicity study with DPGME was used

⁹ From an OECD guideline (414) dermal developmental toxicity study in rats.

Overall, it can be concluded that members of the P-series category are not selectively toxic to the developing rat or rabbit conceptus, even at the high doses used in these studies and even if those high doses produced toxicity in the dam. Where data are available, there is no evidence that the acetates have a different profile for developmental toxicity than the parent glycol ethers.

Reproductive toxicity

Reproductive toxicity studies are available for PGME, PGMEA, DPGEE, DPnGPE, DPGBE and TPGBE-highers. For PGME, an oral 2-generation study in mice (via drinking water) and a 2-generation inhalation study in rats exist. For DPGEE, an oral one-generation study in rats is

available, whereas OECD 421/422 studies via the oral route are available for DPnGPE, DPBGE and TPBGE-highers.

No adverse effects have been observed in the two 2-generation reproductive toxicity studies with PGME. The NOAECs observed in the inhalation study were 300 ppm (1122 mg/m³) for paternal toxicity and 1,000 ppm (3740 mg/m³) for effects on offspring. Sedation and decreased body weight in adults was accompanied by lengthened estrous cycles, decreased fertility, decreased ovary weights and associated ovarian atrophy, reduced pup survival and litter size, slight delays in pubertal indices, and histological changes in the liver and thymus (in offspring) at the highest concentration tested (3000 ppm). However, the nature of these effects and the close correlation with decreased maternal body weights suggest that these effects were secondary to general toxicity and/or nutritional stress. In another study, male rats exposed to 200 or 600 ppm PGME via inhalation (6 hours/day for 10 days) showed no effects on the testes.

No reproductive toxicity was observed with PGMEA in an OECD 422 study conducted by oral gavage, up to 1000 mg/kg bw/day). With DPGEE, no effects on reproduction parameters were observed in a one-generation study (OECD 415, oral route: NOAEL >1000 mg/kg). A screening reproductive toxicity study with DPnPGE (OECD 421, oral gavage) did not result in any reproductive toxicity up to 300 mg/kg. At the highest dose tested (1000 mg/kg), a slight increase in post-implantation loss was observed, related to parental toxicity at that dose level. In an OECD 421 study with DPGBE (oral gavage, up to 1000 mg/kg) no effects were observed. In an OECD 422 study with TPGBE-Highers (oral gavage, up to 500 mg/kg), no fertility effects were observed.

The results from repeated dose toxicity studies, which are available for all P-series glycol ethers, indicate the absence of any adverse effects on reproductive organs. In particular, no toxicity to the testes, no reduction in testicular weight, no damage to the sperm or sperm-producing cells, and no damage to the epididymis or seminiferous tubules has been observed. Likewise, no damage to female reproductive organs was found. Results from studies with members of the category, supported by repeated dose data, do not indicate a potential for reproductive toxicity.

Therefore, since there is no evidence that reproductive toxicity is of concern for any member of the P series, the 2-generation reproductive toxicity study with PGME can legitimately be used for read-across to those members in the category for which no studies exist.

SUBSTANCE	REPRODUCTIVE TOXICITY STUDIES - IN RATS	
	unless otherwise indicated	
<i>Mono-alkoxy Glycol Ether</i>	Oral (rat) NOAEL (mg/kg/day)	Inhalation (rat) NOAEC (mg/m ³)
PGME	1885 ¹ (mice)	3740 ⁵
PGMEA	> 1000 ²	n.a.
PGEE	n.a.	n.a.
PGEEA	n.a.	n.a.
PGnPE	n.a.	n.a.
PGBE	n.a.	n.a.
<i>Di-alkoxy GE</i>		
DPGME	n.a.	n.a.
DPGMEA	n.a.	n.a.
DPGEE	> 1000 ³	n.a.
DPGnPE	300 ⁴	n.a.
DPGBE	> 1000 ⁴	n.a.
<i>Tri-alkoxy GE</i>		
TPGME	n.a.	n.a.
TPBGE	n.a.	n.a.
TPBGE -highers	500 ²	n.a.

n.a. = no data available

¹ NOAEL for off-spring in 2-generation reproduction toxicity study in mice

² NOAEL from an OECD 422 study

³ NOAEL for off-spring in a one-generation reproduction toxicity study in rats

⁴ NOAEL from an OECD 421 study

⁵ NOAEL (1000 ppm) for off-spring in 2-generation reproduction toxicity study in rats

Carcinogenicity

Inhalation studies with propylene glycol methyl ether (PGME) were undertaken in rats and mice exposed to 0, 300, 1,000 or 3,000 ppm vapour (1,100, 3,700 or 11,200 mg/m³) for 2 years, to characterise its chronic toxicity/carcinogenicity. Primary treatment-related effects included: initial sedation of animals exposed to 3,000 ppm; elevated mortality in high-exposure male rats and mice; elevated deposition of α_{2u} -globulin and associated nephropathy in male rat kidneys and increased occurrence/severity of eosinophilic foci of altered hepatocytes in male rats. No toxicologically relevant, statistically significant increases in neoplasia occurred in either species. A numerical increase in the incidence of kidney adenomas occurred in intermediate-exposure male rats; however, the association with α_{2u} -globulin nephropathy, a male rat specific effect, indicated a lack of relevance for human risk assessment. Therefore PGME is not considered to be carcinogenic (Spencer et al, 2002).

PROPERTY:	CARCINOGENICTY - INHALATION NOAEC (mg/m3)			
Number of PO units	Alcohol chain length			
	Methyl	Ethyl	Propyl	Butyl
Mono	11058 ¹	n.a. ²	n.a. ²	n.a. ²
Di	n.a. ²	n.a. ²	n.a. ²	n.a. ²
Tri	n.a. ²			n.a. ²
Tetra (highers)				n.a. ²
Mono-acetate	n.a. ²	n.a. ²		
Di-acetate	n.a. ²			

n.a. = no data available

¹ Inhalation studies with PGME with were undertaken in rats and mice

² in the REACH dossier, read-across from the studies with PGME was used

4. Overall evaluation and conclusions

The aim of this section is to confirm the trends and indicate whether there are sufficient data on the category members to support the use of read across where data are missing. In addition, it needs to be stated how read across will be done for the endpoints – e.g. read across from glycol ether to acetate, read across from PGME to all the category members for reprotox, etc.

4.1 Physicochemical properties

Most of the physicochemical endpoints are available for the members of the category. All of the end points show clear and expected trends across and down the category, including for the more important end points such as the vapour pressure and partition coefficient. Some end points show almost constant values across the category. Category members are liquids with very high water solubility, high boiling points, low freezing points and moderate to low vapour pressure. Propylene glycol ethers are soluble in both aqueous and organic solvent systems. The data on the physicochemical properties support the conclusion that in biological systems the substances will behave in a similar manner regarding uptake and distribution (and environmental distribution).

4.2 Environmental fate

There are sufficient data on all the category members to characterise their environmental fate. Category members have a limited tendency to volatilize, partitioning instead to water and soil (based on low Henry's Law constants). The photodegradation data indicate that the P-series glycol ethers will rapidly decompose in the atmosphere under the influence of light. All category members are readily biodegradable, with the exception of di-propylene glycol methyl ether acetate which is inherently biodegradable. Therefore none of the category members would persist in the environment.

4.3 Ecotoxicity

There are sufficient ecotoxicity data to adequately characterise the environmental hazards of all members. Where data exist, they indicate that the propylene glycol ethers present a low toxicity hazard to aquatic species. No major toxicity differences are observed in either the chain-length of the glycol moiety (i.e., whether mono-, di-, or tripropylene) or the type of alcohol to which the glycol is conjugated. The acetates show somewhat higher toxicity (lower LC50s) to fish than the ethers but do not show higher toxicity to *Daphnia* than the ethers. Although modelled algal species data indicate moderate toxicity for DPMA and PMA, this is in contrast to the measured data for PMA, which shows low toxicity. This class of chemicals does not show specific toxic mechanisms. Toxicity is via non-specific narcosis and is directly proportional to the partition coefficient of the substance. This is supported by the fact that toxicities across all trophic levels are within a similar order of magnitude. Due to the non-specific narcosis mode of action and the consistent low order of toxicity across the category, the use of read across via interpolation from adjacent category members to complete the datasets for individual members is considered justified. The use of QSAR tools such as EPIWIN is also considered to be an acceptable

methodology for addressing the few data gaps with the results being typically more conservative than measured data.

4.4 Mammalian toxicity

Acute toxicity

There are acute oral toxicity data available for all category members. These data support the conclusion that category members have a low order of acute toxicity. With one exception (Tetra Highers) the members of this category are not classified for acute oral toxicity. Data exist for several of the category members for acute inhalation toxicity. Typically data are not available for those members with low volatility. Where data exist, there is a low order of toxicity, with the LC₅₀ being greater than the classification and labelling cut off, or greater than the highest attainable vapour concentration. Where oral and inhalation data exist, with the exception of some CNS depression, there is no evidence of a difference in acute toxicity potency. As such, it is concluded that acute toxicity of the category members does not vary via with the route of exposure. The non-specific depression of the central nervous system (CNS) observed with some of the members is typical of many solvents. With some exception (propylene glycol ethyl ether and its acetate) every category member has data on acute dermal toxicity, demonstrating a low order of dermal toxicity. In the case of PGEE and its acetate, the use of read across from the propylene glycol methyl ether or propylene glycol methyl ether acetate is considered justified to address the endpoint due to the consistency across the category regarding dermal toxicity and would be associated with negligible uncertainty.

Skin irritation

Data are available for all category members. The majority of the P-series glycol ethers do not meet the criteria for classification with skin irritation properties; however, as with other solvents, prolonged or repeated skin exposure may lead to moderate or severe skin irritation. No read-across is required for this endpoint.

Eye irritation

The majority of the P-series glycol ethers do not meet the criteria for classification as eye irritant. No read-across is required for this endpoint as information is available for all category members.

Skin sensitisation

Adequate data are available on the category members to conclude that this group of substances do not have skin sensitising potential. The absence of skin sensitising potential also makes it highly unlikely that these would be respiratory sensitisers. Given the consistency across the category, the use of read-across to address this endpoint is considered acceptable and would be associated with negligible uncertainty.

Repeated dose toxicity

Glycol ethers have been extensively investigated for their specific toxicity profiles and target organs following repeated administration. Studies have been conducted in a variety of laboratory animal species, by different routes of exposure and exposure durations.

Generally, the target organs and toxicity profiles of all glycol ethers are detectable shortly after administration. There is not much difference between the effects following sub-acute (up to 28

days) and sub-chronic (up to 90 days) exposure, either in qualitative or in quantitative terms. Administration routes are of little importance for the effects observed. The liver has frequently shown an increased weight, in the absence of significant pathological changes, following high doses of propylene-series glycol ethers. This has been interpreted as an adaptive change, likely to be associated with liver enzyme induction. Kidney weight changes and histopathological changes have been identified following propylene glycol methyl ether and di-propylene glycol ethyl ether administration. Specific research with these glycol ethers has shown that these changes are associated with the accumulation of α_2 -globulin. These effects occurred only in male rats and are considered not to be relevant for humans.

Developmental toxicity

The propylene glycol ethers in commerce have not shown any adverse effects in developmental toxicity studies, either via the oral, inhalation or dermal route. Although for some members of the category studies are lacking, developmental toxicity data are available for each of the different alcohol groups – methyl, ethyl, propyl and butyl. The data also demonstrate that increasing the alcohol chain length does not increase developmental toxicity, neither increasing the PO units does. There are also no significant differences in developmental toxicity between species.

Overall, it can be concluded that members of the P-series glycol ethers category are not developmentally toxic in rats or rabbits. Where data are available, there is no evidence that the acetates have a different profile for developmental toxicity than the parent glycol ethers.

There are sufficient data for the category members to apply read across to fill data gaps for those glycol ethers for which no specific data for this endpoint exist. Read across can be applied from mono- to di- to tri-glycol ethers as well from alcohol to alcohol. The rapid metabolism of the acetates to their parent glycol ethers (see below) justifies the use of read across also for these substances.

Reproductive toxicity

Reproductive toxicity studies are available for a limited number of P-series glycol ethers (PGME, PGMEA, DPGEE, DPGMEA and TPBGE-highers). The category members that have been tested for reproductive toxicity have not shown any adverse effects on fertility.

Since all category members have undergone repeated dose toxicity testing at substantial doses with extensive histopathology, conclusions can also be drawn from these studies regarding damage to reproductive organs. Results from these repeated dose tests indicate that none of the category members caused toxicity to the testes. Specifically, no reduction in testicular weight, no damage to the sperm or sperm-producing cells, and no damage to the epididymis or seminiferous tubules were reported. Likewise, no damage to female reproductive organs was found.

Using a weight of evidence approach, it can be concluded that propylene glycol ethers do not have a potential for reproductive toxicity. Therefore, it can be justified to use the 2-generation reproductive toxicity study with PGME for read-across to those members in the category for which no studies exist.

Genotoxicity and carcinogenicity

It is recognised that the glycol ethers of the P-series category lack specific determinants for either genotoxicity or carcinogenicity. The overwhelmingly negative results obtained in conventional genotoxicity assays, both *in vivo* and *in vitro*, confirm the lack of genotoxic activity for the category. The lack of carcinogenic potential is consistent with the absence of a genotoxic potential and has been confirmed by long-term studies with 2-propylene glycol 1-methyl ether. Glycol ethers of the P-series category do not pose a genotoxic or carcinogenic risk to humans.

Absorption, Distribution and Metabolism

The P-series category of glycol ethers share common paths of adsorption, distribution, metabolism and elimination.

Glycol ethers are readily absorbed following oral administration or inhalation. Dermal absorption is also an important exposure route. It can be expected that there is a clear trend of increased dermal penetration with decreasing molecular size. Once absorbed, P-series glycol ethers are readily distributed throughout the body; no substantial bioaccumulation of the parent compound has been observed.

The potential of the glycol ethers to penetrate the skin makes the dermal route a potentially significant route of exposure for humans. The available toxicological data show that the dermal exposure to glycol ethers does not result in a different toxicity profile than exposure following oral administration. The dermal route is, therefore, an acceptable dose route for hazard characterisation and data generated from dermal toxicity studies would be adequate for addressing the potential hazards of glycol ethers.

The available data on metabolism shows that these substances generally share the same overall metabolic pathway, with similar metabolites being produced. This provides the support to the overarching hypothesis that they will all have similar toxicological properties.

4.5 Conclusions

An extensive data base is available for the members of the propylene glycol ethers category. Data on all relevant endpoints are available for the category.

The propylene glycol ethers are of low environmental concern. None of the members is classified for effects on the environment nor would be considered to be persistent, bioaccumulative or toxic.

The propylene glycol ethers show low acute toxicity by the oral, inhalation and dermal routes of exposure. With a few exceptions, the propylene glycol ethers (and their acetates) are not irritating to skin and eye, and none are showing a potential to cause sensitisation.

The P-series category of glycol ethers share common paths of adsorption, distribution, metabolism and elimination. The available data on metabolism shows that these substances generally share the same overall metabolic pathway, with similar metabolites being produced. This provides the support to the overarching hypothesis that they will all have similar toxicological properties.

Repeated dosing resulted in toxicity generally only at levels > 400 mg/kg in oral studies and > 1200 mg/m³ in inhalation studies and consisted of increased organ weights (liver and kidney) without accompanying histopathology.

Results from available reproductive toxicity studies (including 2-generation, 1-generation and screening studies) together with repeated-dose toxicity studies, in which no toxicity on reproductive organs was found, demonstrate an absence of reproductive toxicity in this category. There are sufficient data available on category members to support the conclusion that they are not developmentally toxic.

Using a weight of evidence approach, it can be concluded that propylene glycol ethers do not have a potential for reproductive toxicity. Therefore, it can be justified to use the 2-generation reproductive toxicity study with PGME for read-across to those members in the category for which no studies exist.

In vitro and *in vivo* genotoxicity studies were negative, indicating that propylene glycol ethers are not genotoxic. When tested in a lifetime study with rats and mice, PGME did not cause an increase in the incidence of tumours.

It is concluded that adequate information for P-series glycol ethers exists for the purposes of REACH to correctly estimate their potential hazards. Available data for the category members indicate that their aquatic and mammalian toxicity is low. Read across therefore would not lead to miss-characterisation of the potential hazards. Where specific data for some members are missing, the use of read across is considered supported and justified. Because of the low toxicity profile and characterization of effects across the group, read across can thus be appropriately utilized.

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Appendix

End points for which read-across is used in REACH registration dossiers

Substance	End point	Substance used to fill data gap
PGME	No read-across used for any end-point	
PGMEA	Sub-chronic toxicity by the inhalation and dermal route	PGME
	Reproduction toxicity	PGME
	Carcinogenicity	PGME
PGEE	Acute dermal toxicity	PGME
	Skin sensitisation	PGME
	Sub-chronic toxicity by the oral route	DPGEE
	Sub-chronic toxicity by the dermal route	PGME
	Reproduction toxicity	PGME
	Carcinogenicity	PGME
	Acute fish toxicity	DPGEE
	Acute Daphnia toxicity	DPGEE
	Chronic fish toxicity	DPGEE
	Chronic Daphnia toxicity	PGMEA
PGEEA	Acute dermal toxicity	PGME
	Sub-chronic toxicity by the oral and inhalation route	PGEE
	Sub-chronic toxicity by the dermal route	PGME
	Reproduction toxicity	PGME
	Carcinogenicity	PGME
	Chronic fish toxicity	PGMEA
	Chronic Daphnia toxicity	PGMEA
PGnPE	Reproduction toxicity	PGME
	Carcinogenicity	PGME
PGBE	Reproduction toxicity	PGME
	Carcinogenicity	PGME
DPGME	Reproduction toxicity	PGME
	Carcinogenicity	PGME
DPGMEA	Reproduction toxicity	PGME
	Carcinogenicity	PGME
DPGEE	Reproduction toxicity	PGME
	Carcinogenicity	PGME
DPGnPE	Reproduction toxicity	PGME

	Carcinogenicity	PGME
DPGBE	Reproduction toxicity	PGME
	Carcinogenicity	PGME
TPGME	Reproduction toxicity	PGME
	Carcinogenicity	PGME
TPBGE	Reproduction toxicity	PGME
	Carcinogenicity	PGME
TPBGE -highers	Acute fish toxicity	TPBGE
	Acute Daphnia toxicity	TPBGE
	Sub-chronic toxicity by the oral route	TPBGE
	Reproduction toxicity	PGME
	Carcinogenicity	PGME